

# The Point

A newsletter for and about the people of the  
**U.S. Army Medical Research  
and Materiel Command**  
**Autumn 2011**



## Are Quick Learners at Higher Risk of Post-Traumatic Stress? And More Importantly, What Can We Do About It?

*Psychiatry experts came together in a recent national workshop to share ideas for more effective rehabilitation of the brain after trauma.*

What do we do with a study showing that higher memory and vocabulary scores on cognitive tests seem to be associated with a higher risk of experiencing post-traumatic stress symptoms? Could research on this subgroup of quick learners who can't seem to lose the memory of a traumatic event provide insights that could lead to treatment possibilities? Discussions such as this were enlightening as psychiatry and neurology experts shared their findings at a recent national military medical research workshop.

Leading civilian and military researchers explored the state of knowledge related to brain dysfunction in an effort to increase progress in preventing and treating mental injury related to combat. The event was funded by the U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center.

Dr. Robert Ursano of the Uniformed Services University of the Health Sciences presented the idea that the medical community must start treating post-traumatic stress more as we do a "common cold" thus reducing the stigma that prevents so many from seeking help. "It's a natural reaction," he said. "But we need to understand

why it becomes chronic in some individuals." Ursano and co-investigator Dr. Murray Stein of the University of California, San Diego, were recently awarded the largest National Institute of Mental Health grant ever given for the study of suicide in the U.S. Army.

Ursano noted that neurobiological reactions to stress indicate a number of different research directions and that

defining PTSD is the key to developing effective therapies. "For instance, if we look at PTSD as an inability to digest early stress symptoms and return to homeostatic balance, it may be best to study the startle reaction. If we think it's an altered set point, examining the cerebellum's role may



Mental issues, including post-traumatic stress, are the second most common reason for medical encounters in the military.



be best. We could even think of PTSD as an autoimmune disorder in which the neurocognitive ability to identify with others, which is usually helpful in social interactions, leads to distress because of such intense identification with others' pain."

Dr. Roger Pitman of Harvard Medical School presented findings from the large-scale psychobiologic twin study he has been conducting for the past 15 years. He is comparing Vietnam veterans with their nondeployed siblings to determine whether biomarkers for PTSD represent a genetic risk factor or have been acquired as a result of exposure to a traumatic event. Based on his work, he cautioned: "Investigators can't just assume abnormalities they find in PTSD are caused by trauma. For instance, one of our studies showed that decreased size of the hippocampus, an area of the brain involved in learning and memory, was a familial trait although other

investigators have associated changes here with stress. It's the physiological responses, such as an increased heart rate after startling stimuli, that seem to be the most reliable acquired markers of PTSD."

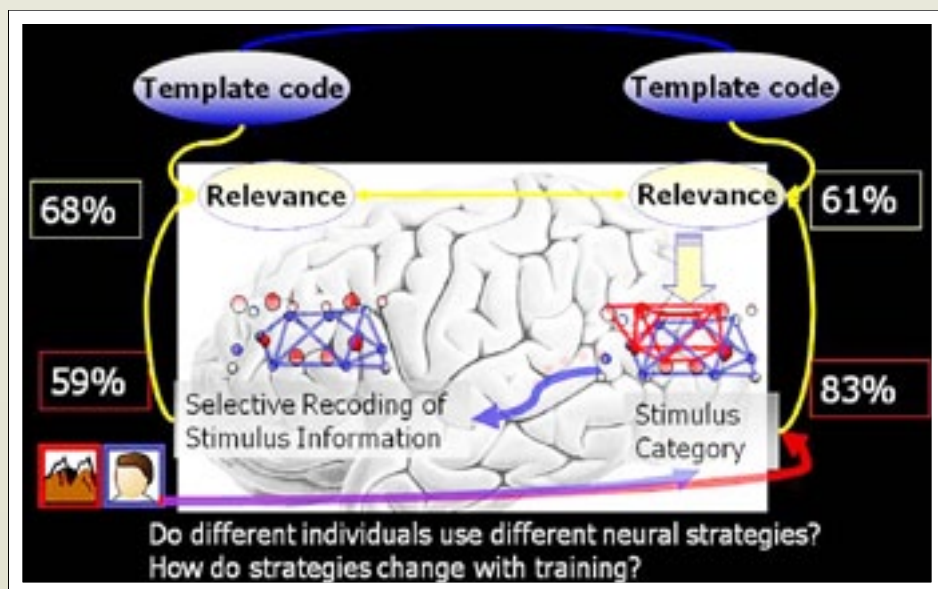
Pitman noted that the most replicated neuroimaging finding in PTSD is a diminished activation of the prefrontal cortex. The theory is that this brain region fails to inhibit the amygdala, an emotional processing center in the brain, thereby preventing extinction of the intense emotional reaction to trauma. In fact, exposure therapy, in which an individual is gradually exposed to fear triggers in a safe setting, is known to be effective in treating PTSD symptoms in many cases. Pitman held out hope that promising drug interventions may come as researchers discover the molecular basis for the strengthened connections in the amygdala that seem to support the emotional response in PTSD.

Dr. Thomas Neylan, director of the Posttraumatic Stress Disorders Clinical and Research Programs at the San Francisco Veterans Affairs Medical Center, presented a discussion on the vital role sleep could play in recovery from injury. According to Neylan, sleeplessness is the most common complaint in both mild brain injury and PTSD, affecting quality of life and functioning. And, in what could be a vicious cycle, the frontal lobes of the brain—those cognitive regions that can temper emotional reactions—are negatively affected by sleep loss.

Because studies have shown that those with PTSD report sleep disturbances while objective measures of their sleep/wake patterns sometimes appear normal, Neylan hypothesizes that their brains are hyperaroused and vigilant even during sleep. He is exploring the possibility of promoting sleep by antagonizing the brain's receptors for corticotrophin-releasing factor, a type of neurotransmitter involved in anxiety-related arousal control. He hopes that his tests of a CRF antagonist may lead to safer sleep medications.

Another approach to helping those who are coping with brain dysfunction, regardless of the cause, was presented by Dr. Anthony Chen, director of the University of California's and VA's collaborative Program in Rehabilitation Neuroscience. His research focuses on theory-driven rehabilitation, developing targeted cognitive training along with ways to measure the outcomes.

Because many individuals with physical or experiential brain injuries have difficulty with cognitive functions crucial for accomplishing goals (e.g., learning, paying attention, remembering, and problem solving), his team developed training techniques



Dr. Anthony Chen is developing techniques to improve cognitive functioning, testing outcomes through performance on neurocognitive tasks and real-world functional tasks, and determining neural mechanisms of successful improvements through the application of functional magnetic resonance imaging biomarkers.

*Image courtesy of Dr. Anthony Chen*



to enhance goal-directed cognition. Chen is measuring effects through a combination of performance on neurocognitive tasks and real-world functional tasks, and determining neural mechanisms using functional magnetic resonance imaging biomarkers. By decoding the brain's cortical activity patterns, he is able to better understand the coordinated neural processes involved in goal-directed control, providing a foundation for developing more effective interventions to improve cognitive functioning.

*TATRC partners with other USAMRMC units such as the Combat Casualty Care Research Program and the Military Operational Medicine Research Program to provide important leadership in military-focused medical research efforts in several areas. For more information on TATRC's research funding and collaborative opportunities, visit [www.tatrc.org](http://www.tatrc.org).*

*Barb Ruppert  
TATRC science and  
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## New USAMRICD Mass Spectrometry Laboratory Features the Latest in Technology

The U.S. Army Medical Research Institute of Chemical Defense recently introduced its newest mass spectrometry laboratory, housing a state-of-the-art Waters Corporation SYNAPT G2 high-definition mass spectrometer. The introduction of this new capability represents a giant leap in the institute's efforts to protect the Warfighter and civilians against chemical and biological threat agents.

The mass spectrometer is a hybrid quadrupole time-of-flight instrument combined with an ion mobility sector, which is capable of electrospray ionization or matrix-assisted laser desorption/ionization. The Q-TOF allows detection of high molecular weight compounds, and the ion mobility sector provides the unique

capability of separating compounds that have identical molecular mass. This coupling of all the different MS techniques into one instrument makes this spectrometer a very versatile research tool and broadens the scope of projects possible. Additionally, the mass spectrometer can be coupled to either a nanoliquid chromatograph, for use with limited sample volume, or an ultraperformance LC, for use with samples in the microliter range.

This newest hybrid ion mobility mass spectrometer will give the institute's investigators unprecedented capabilities to study the effects of chemical warfare agents on the molecular mechanisms and to subsequently identify potential pretreatment and therapeutic compounds.

One of the instrument's most unique aspects is the capability to analyze intact tissue that has been mounted on a slide. Traditionally, MS studies analyze tissue samples that are prepared by techniques that disrupt the tissue's three-dimensional structure and can only confirm that the drug or analyte of interest is in the tissue.

Maintaining the three-dimensional structure during MS analysis allows a researcher "to understand where in the tissue the drug of interest or the peptide or protein of interest is located," said Dr. Frank Zydel, who is a member of the institute's Analytical Chemistry Team in the Medical Diagnostic and Chemical Branch as well as the spectrometer's principal operator.

"So if you want to trace the onset of some injury," explained Zydel, "and how that proteomic cascade happens throughout tissue—where it starts, where it ends, where it migrates to—a drug, a treatment, a pretreatment—you can do it [with this instrument]."

For Zydel, an important advantage to the new mass spectrometer will be its ability to enlighten investigators about mechanisms or pathways about which they were previously unaware.

Sometimes, admitted Zydel, "we don't know what we don't know, and techniques like this will help us dig into what we don't know."

As an example, future plans are to use the data from the two-dimensional images produced by the MS to construct a three-dimensional image, which, said Zydel, "you can literally rotate, look in and out of the tissue, so you can see what is going on where



Dr. Benedict Capacio (left, foreground) explains the unique capabilities of the SYNAPT G2 high-definition mass spectrometer to Dr. Gerald Parker, the deputy assistant to the secretary of defense for chemical and biological defense, and Dr. Ben Petro, the principal director for chemical and biological defense, who happened to be visiting USAMRICD on the day the new lab opened. Col. Deborah Whitmer (background, left), USAMRICD's deputy commander, and Col. Peter Schultheiss, commander, accompanied the visitors. Inset: the simple, sleek design of the high-definition mass spectrometer belies its powerful technology.

*Photo by Darrell Jesonis, USAMRICD*



and when through time-course studies, to help us really identify what we don't know."

According to Dr. Benedict Capacio, the team leader, the instrument is tuned for their first project, looking at protein digests to examine binding sites for various chemical warfare agents. Additionally, projects involving the MALDI imaging of brain slices are scheduled to determine the changes in protein that result from neuropathologic insult from nerve agents.

While the Analytical Chemistry Team has already begun working with USAMRICD investigators to enhance various research studies, they are also looking for projects beyond the institute's doors. USAMRICD is looking forward to this new research capability providing the groundwork to foster collaborations within APG as well as with academic institutes and industry partners, nationally and internationally, interested in studying the mechanisms of chemical warfare agent injury and identifying potential countermeasures for the Warfighter.

*Cindy Kronman  
USAMRICD Public Affairs*

## CDMRP Welcomes New Director



Maj. Gen. James Gilman, Commanding General of the USAMRMC, congratulates Lt. Col. (P) Jeffrey Leggit, new director of CDMRP.

*Photo by Dave Rolls*

As a new director takes the lead at the Congressionally Directed Medical Research Programs, he pledged to continue the work done by his predecessor.

Lt. Col. Jeffrey Leggit, M.D., officially became director of the CDMRP at a Change of Responsibility ceremony Aug. 26. Leggit replaced Navy Capt. E. Melissa Kaime, M.D., who served as director of the CDMRP for three years.

"It is presumptuous for me to think that the growth in research funding and programs, the continued sterling reputation, the state-of-the-art business processes, and the depth of expertise that embodies CDMRP is something I can take credit for," Kaime said. "I simply sustained the trajectory of success that began long before me."

Prior to her tenure at the CDMRP, which also included three years as deputy director, Kaime was the director of the Breast Health Center at the Naval Medical Center in San Diego. She also served in Operation Iraqi Freedom providing trauma care for

U.S. and coalition forces, insurgents, and civilians in Fallujah and Al Asad.

Under Kaime's leadership, annual congressional allocations to the CDMRP for medical research grew from \$368 million in fiscal year 2005 to \$620 million in FY10. The number of awards also rose, peaking at 937 in FY09. She promoted innovative research funding mechanisms, team science, and public transparency while nurturing strong relationships with researchers, clinicians, and consumer advocates.

Leggit joined the CDMRP in May 2010 after serving for nearly three years as director of the Barquist Army Health Clinic at Fort Detrick.

"My intent is to continue to provide excellence in research administration, which has been the tradition here at CDMRP," Leggit said. "Our mission has and will not change; we provide hope."

*David Cline  
CDMRP*

## An End to the Travel Bug?

*Experimental vaccine might someday thwart traveler's diarrhea.*

Of the 50 million visitors to developing countries each year, as many as 60% contract diarrhea with 20% requiring bed rest and 1% hospitalization. While most diarrhea is acute (lasting up to four days), approximately 8%–10% of sufferers may go on to develop persistent or chronic diarrhea.

But traveler's diarrhea (also known as turista) is more than just an unwanted souvenir. It poses a major threat to deployed troops. In fact, it is the most often reported illness among troops in Iraq and Afghanistan, nearly two-thirds of whom reported at least one episode during deployment, half of those requiring medical care. A unit-wide outbreak can waylay troops for days in treatment and recovery thus jeopardizing combat and humanitarian missions.

The principal culprit is enterotoxigenic *Escherichia coli*, a microscopic stowaway that hitches a ride most often in food and sometimes in water. Once swallowed, it begins its covert voyage to the intestines, where it finds a home base as quickly as possible, before the intestines can show this uninvited guest the back door so to speak. There it throws a toxic luau, complete with cramps, nausea, watery diarrhea, and sometimes fever. All you can do is hang in there, keep drinking fluids, and wait for your guest to vacate.

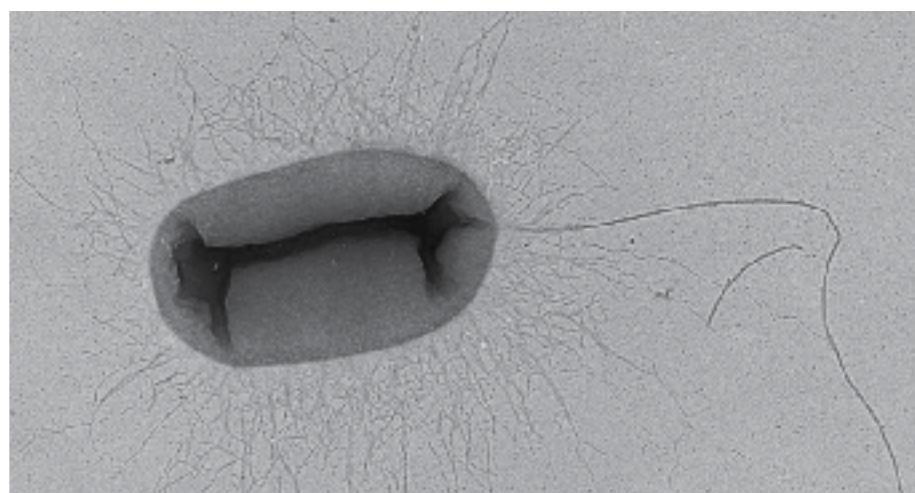
As of yet, there is no vaccine; however, for years researchers have been developing a way to outwit this bug and slam the door on ETEC and they are getting closer.

This summer the U.S. Food and Drug Administration cleared the ETEC vaccine for its first-in-humans clinical trial. Fielding a vaccine requires considerable resources and expertise not to mention adept coordination among governmental agencies and often other entities. For this particular study, the Walter Reed Army Institute of Research, a subcommand of the U.S. Army Medical Research and Materiel Command at Fort Detrick, Md., and the Naval Medical Research Center will conduct the trial in-house, partnering with the Military Infectious Diseases Research Program and the U.S. Army Medical Materiel Development Activity—both subcommands of USAMRMC. MIDRP will spearhead funding and program management, and USAMMDA will provide regulatory oversight.

WRAIR is seeking 40 healthy adult volunteers to proceed with a Phase 1 clinical trial to determine whether the vaccine is safe and will trigger beneficial immune responses.

“Primary outcomes for this trial are safety,” added Cmdr. Mark Riddle, the principal investigator and a researcher in NMRC's Enteric Disease Department. “We hope that the vaccine will be safely tolerated and not result in any severe or serious adverse events. An additional outcome is immunogenicity. We hope that this trial will demonstrate that the vaccine given by the skin will result in robust immune responses and specifically immune responses in the gastrointestinal tract.”

Riddle is proud of the multidisciplinary scope of the ETEC vaccine research effort. “Our team includes



In this electron micrograph, hairlike fimbriae radiate from the surface of an ETEC bacterium. Each hair is tipped with adhesin, a small, sticky protein that enables this dangerous microbe to anchor to the host intestine and begin infection. Turning the tables, NMRC scientists have discovered ways to use this adhesin against the bacterium. By tweaking genes, researchers have devised methods to churn out the adhesin and use it as a vaccine to prevent ETEC anchoring and illness.

*Photo courtesy of Pathology/NMRC*





biochemists, microbiologists, physicians, program managers, epidemiologists, statisticians, and clinical trial coordinators with decades of experience,” he explained.

“The study will cost around \$400,000,” said Lt. Col. David Heath, an office scientist at MIDRP. “Funding ultimately comes from the Assistant Secretary of the Army for Acquisition, Logistics, and Technology.”

It is a lengthy but necessary process from floating the trial’s proposal to securing funds. After researchers submit a proposal to MIDRP, the American Institute of Biological Sciences organizes an expert peer review to evaluate the merits of the study. The panel scores the proposal based on the science and program relevance. The better the score, the more likely it will be funded.

“In this case,” explained Heath, “the ETEC first-in-humans trial proposal was considered a high priority and was funded.” Heath will coordinate closely with Riddle to keep abreast of the program and its progress.

Julia Donnelly, a regulatory affairs scientist at USAMMDA, was a member of the team that reviewed the

study prior to its submission to the FDA. “The foremost concern for any human trial, but especially a first-in-humans trial, is the health and safety of the individuals participating in the trial of the investigational product,” Donnelly said. “This is not only a regulatory concern; this is an ethical concern.”

Donnelly added that the trial will help identify a safe and immunogenic dose, and that researchers will collect serum from vaccine volunteers to produce reference serum to be used in future studies and assay development.

“All of the data we’ve accrued in preparation for this first clinical trial has been very promising,” said Capt. Stephen Savarino, director of the Enteric Diseases Department at NMRC and head of the research team that developed the vaccine.

The NMRC researchers know that to infect its host, the ETEC bacterium must latch on to the intestines, and those researchers also know the secret to its persistence.

Bacteria are covered with fine hairs called fimbriae. At the tip of each hair, the bacterium deposits a sticky protein adhesin that makes it pos-

sible for these fimbriae to adhere to a complementary host cell receptor, like a cruise ship tethering to a dock. Once the bacterium has pulled into port, it rapidly multiplies and releases the toxin that triggers diarrhea. The bacterium’s success hinges on its ability to tether to the intestinal wall—without that there can be no infection.

The NMRC researchers have developed an experimental adhesin-based vaccine that stimulates the production of antibodies that guard the intestinal wall and effectively block ETEC bacteria at the point of contact, denying them a “port of entry.” The researchers have also created a vaccine molecule that combines the adhesin with a nontoxic derivative of the ETEC enterotoxin, in effect alerting the body to produce both anti-attachment and antitoxin antibodies and further defend against infection. The vaccine being tested is a single-component prototype of what would become a multivalent vaccine designed to immunize against the most common strains of the ETEC bacterium.

*Source material provided by USAMRMC*



# New Technology Quickly Navigates Electronic Health Records to Improve Patient Care and Reduce Costs

*Clinical Looking Glass software tool to analyze patient outcomes will be piloted at Walter Reed this year.*

The Military Health System cares for 9.6 million service members and their families with costs that make up 10 percent of the U.S. military budget. A large portion is spent on care for those with chronic diseases such as diabetes, heart disease, and asthma. Improving both efficiency and health outcomes will have enormous benefits for service members as well as the nation.

Locked within the massive amounts of data being collected in electronic health records today are the keys to improved outcomes and lower costs. If the right analytical tools were available, clinicians could find quick answers as to which treatment options are working best, what measures are preventing hospitalization for chronic diseases, or whether a new drug is causing dangerous side effects.

The Department of Defense is working with a civilian partner to test new analytical software that enables physicians and other users to ask a question and receive a statistically valid answer based in EHR data within minutes. The Clinical Looking Glass application is obtaining results comparable to those that in the past have taken weeks, months, and even years of research along with a team with computational expertise.

CLG was developed at Montefiore Medical Center, a university medical center with four hospitals in Bronx, N.Y. A test project to use CLG with MHS data is being conducted with the U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center, the U.S. Air Force Surgeon

General's Office, and the Navy Space and Naval Warfare Systems Command.

The groups have set up a secure environment to host CLG and evaluate its usability among clinicians in the MHS. CLG is expected to be piloted at Walter Reed National Military Medical Center in Bethesda, Md., in September.

CLG grew out of a small team's drive for information that could possibly control the rampant spread of tuberculosis and HIV at a correctional facility in New York City. Montefiore physician and CLG visionary Dr. Eran Bellin notes that the tool is now a crucial part of Montefiore's quality assurance efforts and a required part of training for internal medicine residents. Among other things, it has been used to monitor the success of a diabetes treatment model, identify those at risk of a fatal reaction to a certain drug used to treat anemia, and publish papers on asthma, HIV, and ER treatment of the elderly.

According to Bellin, "With CLG, we can marshal the huge amounts of data we're collecting through EHRs in order to vastly improve patient care. We've never had a way to analyze and visualize data with such flexibility and ease. CLG also enables clinicians to discover unanticipated events as well as find patterns that may help prevent major health issues."

The screenshot displays the 'Criteria Entry' window of the Clinical Looking Glass (CLG) software. The interface is divided into two main columns: 'Study Group' and 'Comparison Group'. The 'Study Group' column contains sections for 'Enrollment And Target Lab Test', 'Target', 'Risk', 'Demographics', and 'Based On Cohort'. The 'Comparison Group' column has a section for 'Same lab will be used for comparison group'. The 'Enrollment' section includes fields for 'Lab Test' (HEMOGLOBIN A1C), 'Initial Value Range' (9.5 to 25), 'Date Range' (6/1/02 to 6/3/03), and 'Cohort' (all). The 'Target' section has a 'Target Value Range' (0 to 7). The 'Risk' section includes 'Risk Window' (365) and 'Blackout Period' (180). The 'Demographics' section has 'Age Group' (Age >= 65) and 'Gender' (Both). The 'Based On Cohort' section has 'Cohort' (No cohort restriction) and 'Use cohort restriction' (checked). The 'Comparison Group' section has 'Initial Value Range' (9.5 to 25), 'Date Range' (6/1/02 to 6/3/03), 'Cohort' (all), and 'Use cohort restriction' (checked).



Robert Connors of TATRC is managing the DoD project. He notes, “We’ve demonstrated the system to hundreds of military physicians, nurses, and administrators with favorable reviews. The next step is to use it at Walter Reed with real data to conduct quality assurance studies and, ideally, remediate patient care issues at the point of care.”

CLG allows clinical team members to create cohorts (groups of patients sharing common factors) for quality assurance studies with just a few simple computer inputs. Cohorts can be compared statistically in minutes to discover differences in whatever health outcome the user defines. CLG can save these cohorts for further use and produce reports suitable for publication in research journals. Privacy protections are built into the system.

TATRC deputy director Col. Ron Propatich says, “We already know what some of our key costs and problems are. With a tool such as this, Military Health System doctors could, for instance, compare outcomes for different blood pressure medications among our patients to see which of these expensive drugs are really working.”

According to Bellin, no other tool builds longitudinal cohorts on the fly with unlimited temporal relationships, which is what allows for complex queries of data and almost immediate answers.

Bellin says, “Doctors can use CLG for patient remediation management, a new concept that is a core of cost-effective care. They can easily find out whether what they’re doing to treat specific conditions is working, and if not, what they can do differently.”

*Barb Ruppert*  
TATRC science and  
technology writer

## Down-to-Earth, Always Happy, and Always On-the-Go Colonel Retires



The U.S. Army Medical Research and Materiel Command said farewell and good luck to Col. Nancy L. Vause at a retirement ceremony June 5 at the Community Activities Center, Fort Detrick, Md.

Vause served as the director of both the USAMRMC Strategic Partnership Office as well as the Army Medical Department Army Research Laboratory Field Office.

Vause’s journey began with a bachelor’s degree from Texas A&M University, continued on to a master’s degree from the University of Memphis, and culminated in her formal education in the area of audiology with a Ph.D. from Vanderbilt University.

In 1981, Vause received a direct commission as an audiologist after working at the Memphis City Schools Hearing Impaired Program, Jackson State University, and Augusta Speech and Hearing Center. Vause’s many military clinical assignments included chief of Audiology and Hearing Conversation, Eisenhower Army Medical Center, Schofield Barrack Health

Clinic, Brooke, Tripler, and Womack Army Medical Centers. Additionally, she served as the executive officer of the first combat Audiology Task Force during Operations Desert Shield and Desert Storm. On the research end, Vause served as the Auditory Research Team leader at the Human Research and Engineering Directorate, Army Research Laboratory.

Before returning to USAMRMC, Vause served as commander for the U.S. Army Center for Health Promotion and Preventive Medicine-Pacific at Camp Zama, Japan.

Vause received many military awards for her service that include the Legion of Merit, the Order of Military Medical Merit, the Surgeon General’s A Designator, the Military Audiology Association Elizabeth Guild Award, and Secretary of the Army’s Wilber Payne Award for her work on the Combat Helmet study. In addition, she was selected twice as military audiologist Scientific Researcher of the Year.

On a more personal note, Vause enjoys participating in recreational activities, such as scuba diving, sailing, and biking as well as reading and creating stained glass windows. She spends quality time with her two daughters, five grandchildren, and her dog.

The Command wishes Vause the best of luck in her future endeavors.

*Melissa Miller*  
USAMRMC Public Affairs

# Single Protein, Key to Ebola Virus Infection, Could Aid in Drug Design

Research published by two teams of Army scientists and collaborators has identified a cellular protein that plays a critical role in Ebola virus infection. The findings, published online August 24 in separate studies in the journal *Nature*, suggest a possible strategy for combating one of the world's most deadly viruses.

Ebola causes hemorrhagic fever with case fatality rates as high as 90 percent in humans. The virus is of concern both as a global public health threat and as a potential agent of biological terrorism. Currently there are no available vaccines or therapies to combat the disease. In addition, much is still unknown about the exact mechanism by which Ebola virus invades cells and causes infection.

In one *Nature* study, scientists from USAMRIID, Albert Einstein College of Medicine, the Whitehead Institute for Biomedical Research, and Harvard Medical School searched for proteins that Ebola virus might use to enter cells. One such cellular protein, known as Niemann-Pick C1, stood out; the team found that if cells do not make NPC1, they cannot be infected by Ebola virus.

According to the authors, the NPC1 protein is embedded within cell membranes where it helps transport cholesterol within the cell. However, the absence of NPC1 due to gene mutations causes a rare degenerative disorder called Niemann-Pick disease in which cells become clogged with cholesterol and eventually die.

To confirm the group's finding that NPC1 is crucial for Ebola virus

infection, John M. Dye, Ph.D., and colleagues at USAMRIID used mice that were partially deficient in NPC1 expression, challenging the animals with lethal doses of Ebola virus. Remarkably, most of the mice survived the challenge. Other studies using cells from people with Niemann-Pick disease found that those cells also were resistant to Ebola virus infection. In addition, the researchers showed that treating cells with a compound that blocks NPC1 function inhibited infection.

In the second *Nature* article on this topic, another team of USAMRIID scientists, working with investigators from Brigham and Women's Hospital and Harvard Medical School, independently arrived at the same conclusion—that Ebola virus needs NPC1 to enter the cell and cause infection.

The BWH group used a robotic method developed by Harvard's National Small Molecule Screening Laboratory to screen tens of thousands of compounds for activity against Ebola virus. They identified a novel small molecule that inhibits Ebola virus entry into cells by more than 99 percent.

Next, USAMRIID investigators Lisa Hensley, Ph.D., and Claire Marie Filone, Ph.D., verified that the newly identified inhibitor, or compound, blocked cell-to-cell transmission of Ebola virus. Using the inhibitor as a probe to investigate the pathway of infection, they found that the target of the inhibitor is NPC1—the same cell protein described by the other research team. The findings suggest that small molecules that target NPC1

and inhibit Ebola virus infection have the potential to be developed into antiviral drugs.

"The fact that two groups identified the same protein, using two different experimental approaches, is significant," Dye commented. "This independent corroboration greatly increases our confidence in the findings."

Hensley said both studies represent the first step in a promising line of research that could make it possible for scientists to design therapeutics that impede the ability of the Ebola virus to infect and spread.

Both projects received funding support from the Defense Threat Reduction Agency.

The work completed at USAMRIID using authentic Ebola virus was critical for validating the role of NPC1 in Ebola virus infection. This research can only be conducted in maximum containment biosafety level 4, laboratories where investigators wear positive-pressure suits and breathe filtered air as they work.

USAMRIID, located at Fort Detrick, Md., is the only Department of Defense laboratory with BSL-4 capability. The Institute is the lead military medical research laboratory for DTRA's Joint Science and Technology Office for Chemical and Biological Defense and plays a key role in national defense and in infectious disease research.

USAMRIID's mission is to conduct basic and applied research on biological threats resulting in



medical solutions (vaccines, drugs and diagnostics) to protect the warfighter, but its research often has applications that benefit society as a whole. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

For more information, visit [www.usamriid.army.mil](http://www.usamriid.army.mil).

*Caree Vander Linden*  
*USAMRIID Public Affairs*

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2. Small molecule inhibitors reveal Niemann-Pick C1 is essential for Ebola virus infection. Marceline Côté, Anna Bruchez, Qi Li, and Kartik Chandran, Division of Hematology, Department of Medicine, Brigham and Women's Hospital, Boston, Mass.; John Misasi, Division of Hematology, Department of Medicine, Brigham and Women's Hospital, Boston, Mass. and Division of Infectious Disease, Department of Medicine, Children's Hospital, Boston, Mass.; Tao Ren and Kyungae Lee, New England Regional Center of Excellence for Biodefense and Emerging Infectious Diseases, Harvard Medical School, Boston, Mass.; Claire Marie Filone, Division of Hematology, Department of Medicine, Brigham and Women's Hospital, Boston, Mass. and USAMRIID, Frederick, Md.; Lisa Hensley, USAMRIID, Frederick, Md.; Daniel Ory, Diabetic Cardiovascular Disease Center, Washington University School of Medicine, Saint Louis, Mo.; and James Cunningham, Division of Hematology, Department of Medicine, Brigham and Women's Hospital, Boston, Mass. and Department of Microbiology and Immunology, Harvard Medical School, Boston, Mass.



## Loss in Space

*Space Tissue Loss experiment returns from final shuttle mission.*



Byron Waddy (left) and William Santos coating bioreactors in the STL-USAMRMC STS-135 laboratory at the Space Station Processing Facility at Kennedy Space Center.

*Photo courtesy of USACEHR*

Atlantis and its sister space shuttles may be grounded, but the science they helped drive continues on—and up.

On Atlantis' final mission in July, the Space Tissue Loss program, a partnership between NASA and the Department of Defense, sent up an experiment developed by the Walter Reed Army Institute of Research in Silver Spring, Md. Its goal: to study human cellular response to bacteria in microgravity. Microgravity is notoriously hard on a

body, speeding up muscle atrophy and bone density loss. It also compromises the immune system.

"Prolonged residence at the space shuttle causes immunocompromisation in the astronauts, for reasons nobody fully comprehends," said Dr. Rasha Hammamieh, principal investigator of the experiment and deputy director of Integrative Systems Biology at the U.S. Army Center for Environmental Health Research at Fort Detrick, Md.

"Astronauts not only suffer from a delayed healing process, they also become particularly vulnerable to bacterial infection."

USACEHR, a subcommand of the U.S. Army Medical Research and Materiel Command, applies systems biology approaches to study such diseases. Working with Hammamieh on this study are co-investigator Dr. Marti Jett and colleagues Dr. Aarti Gautam and Nabarun Chakraborty.

Hammamieh hopes this experiment will help scientists understand specifically how to treat wounds during spaceflight and long space missions and in extreme environments on Earth. Central to the study are molecular signatures—sets of genes, proteins, genetic variants, or other variables that serve as early warning signals for disease.

"We expect the findings from microgravity to infer some 'blockers' of healing we have not necessarily been able to pinpoint relating to lack of healing in disease states on Earth," said Hammamieh. "This has the potential to lead to novel therapeutics and, perhaps even vaccines, against infectious diseases in the general public. Our research has potential benefits and applications both for life on Earth and astronauts on long-duration space missions."

Researchers have tried replicating the microgravity experiment on the ground, but shuttle experiments contradicted some of their results. Thus space remains the only reliable environment in which to study how microgravity affects cell growth and how cells fight off infections.





Hammamieh and her colleagues had mere months to prepare and pack the experiment aboard the Cell Culture Module, a wholly automated, temperature-controlled incubator system adapted for spaceflight and low Earth orbit. Developed by Hawaii-based Tissue Genesis, the CCM is essentially a laboratory in a box in which to study the effects of microgravity on cell cultures.

“Wound healing is a complex process with many potential factors that can delay healing,” explained Hammamieh. “All chronic wounds are colonized by bacteria. We are studying endotoxin-induced injury on dermal endothelial cells.” Endotoxin is a bacterial toxin that inhibits certain host functions, opening the door to disease. “An endotoxin commonly associated with Gram-negative bacteria was injected into the test samples during the flight, and the reaction was stopped at two different time intervals. A solution was perfused into the cell chamber to preserve the cell responses.”

Hammamieh’s team will study the cell cultures at USACEHR’s laboratory. It could take six months to generate data and another six to analyze the data and draw conclusions.

“With the evolving ‘-omics’ approach in the field of science, we will be able to [generate] copious amounts of data at multiple levels of biology,” said Hammamieh. “Transforming the findings of the present study into an effective therapeutic approach requires additional research steps.”

But to conduct future studies in space, Hammamieh and fellow researchers will have to find a new ride, likely aboard Russian Soyuz space capsules. “The STL program surely has an international future,” said Hammamieh, who sees opportunity in the coming changes. “For instance, over the

years, Russia’s Mir space station was covered by biofilm hosting microbes at microgravity. In fact, microbes were found in the water and air at the Mir space station, which further intensified the risk of having infection even from

minor wounds. In this perspective, our study has a plausible future in the International Space Station Program.”

*Jill Lauterborn  
USAMRMC writer*



STS-135 mission specialist Rex Walheim in the middeck of Atlantis.

*Photo by Capt. Robert Plunkett,  
DoD human spaceflight payload manager, DoD Space Test Program, SMC, SDD/OL-S*



CSTS-135 mission specialist Rex Walheim performing temperature checks of the STL CCM in the middeck of Atlantis.

*Photo by Capt. Robert Plunkett,  
DoD human spaceflight payload manager, DoD Space Test Program, SMC, SDD/OL-S*

## Exercise, Blueberries, and Sleep

*Medical evidence is supporting some natural ways to protect the brain from injury.*

In a national military medical research workshop held in May, experts in several fields related to brain dysfunction gathered together and, among other topics, explored the roles of exercise, diet, and sleep in protecting the brain.

The event was funded by the U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center. The primary goal was to discover how current tools and knowledge could converge to arrive more quickly at real solutions for those injured in combat.

Over the past decade, several studies have highlighted the beneficial effects of exercise on memory and learning. Some investigators, such as those at the University of California, Los Angeles, Brain Injury Research Center, are studying the role of exercise in healing after traumatic brain injury. While they have found that improvement is highly dependent on injury severity and timing, it appears that exercise holds promise as a pos-

sible protective mechanism or means of reducing the effects of traumatic exposure and mild brain injury.

Workshop presenter Dr. Henriette van Praag of the National Institute on Aging explained that until recently it was thought that no new neurons in the central nervous system could be generated after birth, but new research has shown that neurogenesis occurs in the adult hippocampus. This is an area of the brain that plays a vital role in learning and memory; thus, neuronal growth here could conceivably improve cognitive abilities damaged by traumatic exposure.

Van Praag presented her findings on neurogenesis and learning in rats. She has tagged and imaged the growth of new cells in the hippocampus and found that exercise is a strong regulator of neurogenesis, tripling neural growth. In her studies, even aged rats learned faster with exercise.

She also found, in mouse studies, that epicatechin, an antioxidant found in

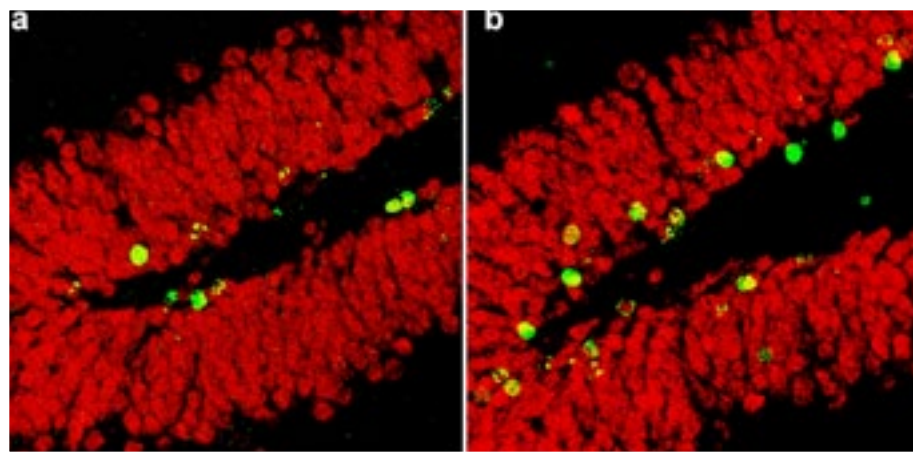
cocoa beans, helped mice remember a task longer and improved the structure of existing neurons in the hippocampus. The effects were enhanced with exercise. Other antioxidants such as flavonol, found in fruits like blueberries and cranberries, have been associated with decreased risk of Alzheimer's and other age-related diseases.

Dr. Star Lee, who moderated one of the workshop's panel discussions, is also studying adult hippocampal neurogenesis and cognitive function. She previously researched the effects of neuroinflammation in adult animals and is currently investigating the impact of diet on neurogenesis in her postdoctoral work at the Salk Institute for Biological Studies. Preliminary findings show that supplementing diets with flavonoids increases newborn neuron survival and enhances spatial memory in aged mice.

Presenter Dr. Alison Cernich adds to knowledge in this field by studying the cognitive effects of cardiovascular exercise after stroke. As the director







Dr. Henriette van Praag has shown that running mice have more new neurons in the hippocampal region of the brain than sedentary controls. Shown here are images of BrdU-positive cells in control (a) and runner (b) mice. Sections were immunofluorescent double-labeled for the marker for newly generated cells, bromodeoxyuridine, BrdU (green), and the neuronal marker, NeuN (red).

*Image courtesy of the National Institutes of Health and Dr. Henriette van Praag*

of neuropsychology at the Veterans Affairs Maryland Health Care System, she presented initial findings that show small gains in cognition among those engaged in a regular aerobic routine.

Workshop participants also discussed how other beneficial effects of exercise, such as improved mood and sleep, could greatly enhance mental health among deployed service members. Dr. Thomas Neylan, director of the Posttraumatic Stress Disorders Clinical and Research Programs at the San Francisco VA Medical Center, noted that sleep disruptions affect brain function, metabolism, and immunity. He shared his findings from a study published last year associating poor sleep quality with a smaller hippocampal volume. If sleep disruptions can negatively affect this region in which new neurons emerge, then perhaps improving sleep conditions or treating sleep disorders can improve neurogenesis and cognitive functions.

Several in the group noted that perhaps protective measures involving exercise, diet, and sleep could be implemented in the military as efficient, effective ways to improve the care of Soldiers. Some pointed out that this research and policy direction should also be accompanied by a shift in thinking in which mild traumatic brain injury and post-traumatic stress are not seen as permanent conditions and labels but as symptoms from which Soldiers can and do recover.

Concluded Cernich, “We can best help our service members if we focus on wellness and treating symptoms, and keep the technology simple.”

*Barb Ruppert, TATRC science and technology writer*

# An Ounce of Prevention and the Extra Mile

*USAMMA oversees the critical mission to deliver vaccines to Soldiers worldwide.*

Bullets and bombs aren't the only threats to Warfighters. Soldiers remain vulnerable to biological attack. The U.S. Army Medical Materiel Agency at Fort Detrick, Md., arms troops with the best possible defense against this threat—the vaccine. USAMMA's agile 14-member team ensures that vital immunogens are safely shipped to base medical facilities that treat nearly 1.4 million service members at 5,000 bases in the United States and its territories and another 700 bases worldwide.

In an age of one-click orders and express delivery, we sometimes forget the world remains a big place. Distance isn't USAMMA's only challenge. Global entities, weather patterns, even the timeless processes of Earth create new hurdles. Dotting the globe are 195 countries—their collective 49,000 airports and 600 ports all vulnerable to natural calamities, such as tsunamis, that disrupt supply chains. Political landscapes also shift, and often. Recent political upheavals in the Middle East and North Africa, for example, have threatened critical supplies of grain and medicine to countries troubled by violence.

Layers of complexity present enormous challenges for the shipping industry and others relying on contractual "guarantees." On paper, USAMMA's intricate relationship with agencies, manufacturers, vendors, and shipping companies is a virtual wiring diagram. Its mission is further complicated by the delicate nature of vaccines. To make it all work requires expertise in scenario and contingency planning, an unyield-

ing commitment to the Department of Defense's standards, and fidelity to troop health, all the while operating with shrinking budgets and resources.

## Born Out of Crisis

As tensions mounted over United Nations inspections in Iraq in the late 1990s, and rumors swirled over possible biological attacks against Soldiers, USAMMA, which oversees medical logistics and provides health service support to the Armed forces, assumed distribution of the anthrax vaccine, from manufacturer to medical facilities.

"We call it 'from requirement to retirement,' meaning we track the package all the way until it reaches its final destination, its customer," explains Lt. Col. Todd Williams, USAMMA pharmacist consultant and director of Support Operations.

Vaccine requests are submitted to a secure database. Once the Services approve a request, they send it to the USAMMA Distribution Operations Center for processing.

"We don't have a big warehouse," Williams explains. "When we stock the product, we partner with the Stra-

tegic National Stockpile. They do all the packing and the shipping for us. But we do all the tracking to make sure it gets to its location. That's our unique specialty. We minimize losses for the DoD. When we see a hiccup, we're there."

USAMMA DOC, which provides supplies and services to the military worldwide, developed the cold-chain management system that follows a strict procedure for handling all vaccines. Sturdy shipping containers have 2 inches of polyurethane foam insulation. Gel packs surround the fiberboard boxes that hold vaccines, and each box is fitted with a temperature-monitoring device known as a TempTale. These multiple fail-safes are designed to keep the product in the critical range of 2°C–8°C (35°F–46°F) for 72 hours, the time frame in which all shipments should reach their destination.

Andrew Brown, the Anthrax and Smallpox Project manager, tasked with distributing to all services, reflects on how far the DOC has come since its inception. "Today, we use carriers and have reliable resources like those monitors right in the pack-

**"We're protecting our Soldiers on the battlefield so we hold to the highest standards." – Lt. Col. Todd Williams, the U.S. Army Medical Materiel Agency pharmacist consultant and director of Support Operations**

**To make it all work requires expertise in scenario and contingency planning, an unyielding commitment to DoD standards, and fidelity to troop health.**



age. Back then if we wanted to make sure it got there, we actually got on a plane with it. Can you imagine the manpower being wasted?”

Since 1998, USAMMA’s mission has expanded to include distribution of vaccines for smallpox and influenza, investigational new drugs, and foreign military sales. Each year, the DOC distributes \$40 million worth of vaccines, including 2.5 million doses for influenza, 1 million for anthrax, and 350,000 for smallpox. The vaccination program’s goal is to erase the threat of these contagious and sometimes fatal diseases and ensure our Soldiers’ health and military readiness.

### Train for Success

With so much at stake, training is a priority. The DOC is an integral part of the DoD’s Military Vaccine Agency, which operates an online information and training site called MILVAX for storing and handling vaccines. The DOC team provides on-site training and consultation and keeps medical facilities informed of all drug expiration dates and manufacturer recalls. It is singularly responsible for educating all parties, from carriers to customers, about the policies and procedures to protect the integrity of vaccines.

To raise their profile and advance their mission, team members reach out in a variety of ways: attending conferences, distributing literature, and hosting briefings. Any staff turnover at the manufacturer, DOC, carrier, or medical facility can wipe out gains in useful knowledge so there’s always a new contact with a familiar question.

“We educate our customer every single day,” says Brown. “We have to make contact every day.”

In addition, the DOC actively scru-



**Highlighted Facts:** 195 countries, 600 ports, 49,000 airports, 5,700 military bases, and 1.4 million service members

USAMMA oversees medical logistics and provides health service support to the Armed forces worldwide.

*Photo by Dave Rolls*

tinizes data to identify and address gaps in training and prevent future vaccine losses.

“We track on the quality control side,” says Williams. “When we notice, for example, in Korea that they’re having some vaccine losses, that’s when we send a team over to provide additional cold-chain management training.”

“If vaccines are indeed compromised, what follows is an intense scramble to replace that supply,” explains Teresa Bess, Flu Program manager.

“We can’t just re-buy,” says Bess. “I have to start pulling from another location. A large loss can be very harmful, even to one’s career. Any installation that does not do what it needs to do is in violation of the Medical Command’s policies, guidance, and regulations. Whatever vaccine is shot into a Soldier’s arm must be good, safe, and effective.”

### The Cold Truth

Overheated vaccines can sometimes be salvaged, but cold is a killer. Temp-

Tale, a temperature-monitoring device manufactured by Sensitech Inc., has been a great boon to the Army. It keeps a record of fluctuations and includes an alarm to alert a carrier that the package might be compromised.

“It monitors the temperature from the time it is packed until it gets to its destination,” says Brown. “It gives you a temperature range throughout that shipment—a high/low, an average, and the time it was at those particular temps. Those monitoring devices have saved the DoD a huge amount of money by reducing loss.”

The TempTale is a DoD-specific requirement, one the docks started regularly using in 1999.

“When we called the FDA,” explains Williams, “we found out [manufacturers] have up to 48 hours to get the package to the site, and no temperature-monitoring device is required by the FDA. But we’re requiring it because we have a stricter standard.

We want to know for sure that the product is reaching its destination in its appropriate temperature range.”

“A lot of companies test their product,” Brown adds. “If it ships or is received at the site within X amount of days, the priority is good. But if you go into different environments—that’s what DoD is looking at. You may be in a cold environment today, and you may be in a hotter environment the next day, and we want to make sure the product is staying within the temperature range.”

## Racing the Clock

Temperature is only one aspect, though. Time is another, and choosing the right courier to expedite a shipment is key. Countries’ regulatory environments vary greatly so it is important the courier has a clear understanding of customs processes and nuances to minimize delays.

“We use a variety of carriers,” says Brown. “If you’re not meeting our requirement, then your service is limited. If I used your service two years ago, that doesn’t mean I’m going to use it right away again. I have to do some test shipments to see if you still can deliver. Not with the actual product—I’m testing the route and how long it would take us to get there, and would it be anything that involved temperature fluctuations. We test the route before we release the actual product. We don’t want to waste it.”

Bess says the DOC regularly pursues cost-effective options. “We started this year using dedicated refrigeration trucks [for shipping the influenza vaccine] because you can hit a lot of locations, especially down here in the Joint Task Force region, instead of doing Fed Ex, Fed Ex, Fed Ex. Those locations get [packages] on pretty

much the same day. And it did save the government money.”

As the DoD’s requirements are stricter, the Defense Logistics Agency makes sure to hammer out every detail in the carrier’s contract.

“If you’re going to ship to DoD,” explains Williams, “we want you to use the cold-chain management principles. We want to make sure [our Soldiers] are protected.”

For those operating outside the safety of a thorough contract, Bess can only offer her sympathy. “I’ve had a couple of the [National Guard states] ask, ‘Ms. Bess, are my vaccines still good?’ Well, I don’t have the answer for them. You have to build [safeguards] into the contract.”

## Ready for Anything

Put together an excellent process, validated packaging, a dependable courier, and a clear route, and the unexpected can still happen.

At no time was this more apparent than March 11, 2011, when an 8.9-magnitude earthquake struck off

the coast of northeastern Japan. The resulting 30-foot tsunami ravaged 1,300 miles of coastline, sweeping away port facilities and burying tarmacs and runways in silt. As events unfolded, shipping companies frantically adapted, accounting for cargo and seeking alternate routes.

“A lot of carriers were trying to avoid Japan,” Brown says. “If I have to go through Manila, then it’s a different process, customs paperwork. And so that is obviously a challenge.”

Certainly such a *force majeure* would limit one’s liabilities, but USAMMA’s sensible and timely reaction in crisis salvaged irreplaceable vaccines. It boils down to having contingency plans in place. The DOC uses several carriers to ship vaccines to the destination. If one carrier is unable to deliver because of a route change, the DOC quickly secures an alternate that can meet the delivery deadline while adhering to cold-chain management procedures.

## An Eye on the Ball

Delivering critical vaccines worldwide on time and intact takes a team



**The Little Agency That Could:** USAMMA’s agile 14-member team ensures that vital vaccines are shipped to any base medical facility, on time, without being compromised. Pictured (left to right) front row: Cheryl Bailey, Kandi Barnhart, Christine Kujawa, Kitty Reese, Teresa Bess, Bonnie Pereschuk, Migeul Rivera, and Andrew Brown; second row: Phillip Marshall, Randy Harris, Lt. Col. Todd Williams, Quinn Hurley, and Terri Ventrone. Dana Lunceford is not pictured.

Photo by Dave Rolls



willing to deal with the myriad of challenges. Whether USAMMA's couriers appreciate it or not, an extra set of eyes is always tracking those vital shipments.

"When we see that package get hung up, we're calling people," Williams says.

"We are constantly on the phone with the carrier or our customer," Brown agrees. "If there's additional paperwork, we either fax it, e-mail it, or figure out the quickest way to get there. Once that package lands, we know, and if the recipient doesn't call us right away, we're on that phone. They say, 'Oh, yeah, I just got it.' Yes, but you need to call to confirm. When our package is not moving, we contact our carriers. We ask why. They say, 'It's on the plane.' But your tracking system is saying it's still here—you need to update your tracking system."

Success requires dogged determination from a dedicated team, 24/7.

"We have a leash," says Brown, holding up a Blackberry. "When we're sleeping, other people are available to receive calls if there are any problems or questions. If we know a package's estimated arrival is midnight our time, then yes, we still track it. And if we don't hear from them, we make the call. We're a small operation, but we produce volume. Some days are more taxing than others. There's never a dull moment."

There are countless long nights resolving logistical issues, particularly during 2009's H1N1 scare. It comes with the territory, says Bess. "You know what gets me through? Loving my military. Each and every one of them deserves the best I can provide. They have such dedication to mission and stand for freedom for all of us. We owe so much to our military for all we have as a country."

*Jill Lauterborn*  
*USAMRMC writer*



**H1N1 Rapid Response:** Responding effectively to the 2009 H1N1 outbreak required seamless coordination. "When we shifted to the H1N1 pandemic plan, we essentially used our flu plan," explains Lt. Col. Todd Williams. "We realized many people didn't even know how the flu worked. So then we had to go and brief all the way up to the Army Chief of Staff about the process." During the crisis, the DOC shipped more than 4 million doses of the H1N1 influenza vaccine worldwide. Pictured (left to right): Lt. Col. Gus Gogue, Spc. Eric Rudolph, Sgt. 1st Class Michael Mills, and Maj. Rory Irwin unload boxes of the H1N1 vaccine at the 424th Medical Logistics Company warehouse at Bagram Airfield in Afghanistan.

*Photo by Dave Rolls*

# USAMRIID Scientist Brings Home Prestigious Award for Work on Lassa Fever Vaccine

When Dr. Kathleen (“Kat”) Cashman heard the title of the best overall scientific poster at the DNA Vaccine Congress announced in San Diego last month, her first reaction was surprise.

“I thought, wow—someone else has a poster about Lassa fever virus, too!” says Cashman with a laugh. Of course, it was her poster’s title being read aloud, and Cashman, upon hearing her name, realized that she had captured the prestigious Hilleman Award, given annually in memory of Dr. Maurice Hilleman, who developed 8 of the 14 vaccines currently used in routine childhood immunizations.

Cashman, a contract principal investigator at the U.S. Army Medical Research Institute of Infectious Diseases, began working with Lassa virus in 2005, when she came to the institute as a postdoctoral research fellow. The virus, endemic in West Africa, causes a severe hemorrhagic fever that is 20 to 50 percent fatal in humans and permanent hearing loss in about one-third of those who survive. The disease also affects health care workers in endemic areas since they may not have access to the equipment necessary to maintain barrier nursing precautions that can keep the disease from spreading.

Cashman especially liked the idea of doing work that could benefit public health as well as protect U.S. service members around the world from a potential biological threat. So she took on a project to develop a Lassa vaccine that relies solely on the genetic code of the virus to provide protection.



Dr. Kathleen Cashman works in a biosafety level 4 laboratory where personnel wear positive-pressure “space suits” and breathe filtered air. These laboratories are specially designed to handle pathogens (including Lassa fever virus) for which no vaccine or treatment has been developed yet. USAMRIID, where Cashman works, is the only Department of Defense laboratory with BSL-4 facilities.

*Photo courtesy of USAMRIID*

DNA vaccines are made by modifying the unique genetic material, or DNA, of an organism such as a virus. This material, when injected into a person, leads to the expression of the genes within the modified DNA and ultimately to the production of viral proteins inside the injected cells. As a result, the person’s immune system responds in a protective manner similar to the response that would occur during an exposure to the virus itself.

Cashman’s vaccine is codon optimized, meaning the gene has been tailored to the individual species to enhance protein expression and improve efficacy. In her initial studies using guinea pigs, she was able to show that all of the vaccinated animals survived challenge with lethal doses of the virus. However, there was a clear difference in delivery methods.

Animals that were vaccinated by a device that delivers the vaccine into the muscle developed fever and were slightly viremic, meaning they had measurable levels of virus in their bloodstreams. In contrast, animals that were vaccinated through the skin using a process called dermal electroporation, or DEP, not only survived but developed no fever and no viremia.

Encouraged by the results in guinea pigs, Cashman designed and conducted a study from January through May 2011 to test the codon-optimized DNA vaccine in nonhuman primates using the DEP delivery method. Not only did all of the vaccinated primates survive infection, they developed no fever and no viremia. Taken together, these research results demonstrate the candidate vaccine’s efficacy in two different animal models of Lassa fever.



According to Cashman, the next steps are determining the minimum effective dose of vaccine in NHPs, developing correlates, or markers, of protective immunity that would be predictive of the vaccine's efficacy in humans, and evaluating the durability of protection induced by the vaccine.

Modest by nature, Cashman seems a bit taken aback by all of the attention she has received but is happy that the significance of the work is being noticed. She has plenty to keep her busy; she recently applied for a joint patent with Inovio Pharmaceuticals, the developer of the delivery system. There is still primate data to analyze, a paper to write, and other studies to design.

"This is a unique opportunity, not just to help Soldiers, but to help people," she says simply. "We have a real opportunity here to do some good."

*Caree Vander Linden  
USAMRIID Public Affairs*



Staff Sgt. Craig Wayman and Sgt. Esther Collins were selected for induction into the prestigious Sergeant Audie Murphy Club on August 4. Induction and membership in the Medical EDCommandOM SAMC is a reward for noncommissioned officers whose leadership achievements and performance merit special recognition. The SAMC is a means of recognizing those NCOs who have contributed significantly to the development of a professional NCO corps and a combat-ready Army. Members exemplify leadership characterized by personal concern for the needs, training, development, and welfare of Soldiers, and concern for families of Soldiers.

## 2011 NCAB/AALAS Technician Award Winner

Lindsey Schwartz, an animal care technician at the U.S. Army Medical Research Institute of Chemical Defense, was awarded the 2011 National Capital Area Branch/American Association of Laboratory Animal Science Technician Award, presented by the Scientists Center for Animal Welfare. Schwartz submitted a paragraph essay on the importance of the animal care technician as a member of the research team. A panel of experts reviewed the essays, and Schwartz' was selected as the standout submission for this year. In recognition of her winning essay, Schwartz received

a two-day registration to the NCAB/AALAS annual educational seminar, one night's hotel accommodations, and a banquet ticket. This year's meeting was held August 31 to September 1 at the Gaylord National Resort & Convention Center at National Harbor, Washington, DC.

SCAW is composed of research professionals dedicated to balancing animal welfare and excellence in basic and applied scientific inquiry.

*Submitted by USAMRICD*



# Virus Hunter

*New rapid-detection device enables public health officials to pinpoint Rift Valley fever.*

## More Deaths from Rift Valley Fever in Saudi Arabia and Yemen

*(The Lancet, October 2000)*

## Rift Valley Fever Deaths in Sudan

*(BBC News, Nov. 15, 2007)*

## Rift Valley Fever Death Toll on the Rise

*(Pretoria News, May 7, 2010)*

## Economic Losses from Rift Valley Fever Greater than Previous Documented

*(ILRI Clippings, Oct. 10, 2010)*

Epidemiologists now have a tool that might make such tragic headlines a thing of the past. The Military Infectious Diseases Research Program, one of the U.S. Army Medical Research and Materiel Command programs, and VecTOR Test Systems have developed a diagnostic device that can detect the presence of the Rift Valley fever virus in mosquitoes, alerting deploying troops to its presence and enabling public

health officials to prevent or mitigate the spread of disease.

RVF is a mosquito-borne viral disease that poses a significant health risk, primarily to livestock, but also to humans. Epidemiologists have been aware of RVF since first isolating the virus in Kenya in 1931. Over the decades, the virus has spread throughout sub-Saharan and North Africa and beyond the continent's borders to Saudi Arabia and Yemen.

Health officials openly wonder whether RVF could strike Southern Europe or even the United States.

Scientists believe the virus persists in nature because infected female *Aedes* mosquitoes transmit it to their eggs. The infected eggs lay dormant until excessive rainfall when they hatch and produce infected adult mosquitoes that can initiate an outbreak. Secondary vectors, such as *Culex* mosquitoes, also reproduce rapidly during heavy rains and contribute to disease outbreaks among animals (known as epizootics).

The most vulnerable human populations are farmers and herders who live near canals, rice fields, and other wet zones where mosquitoes proliferate. In animals, RVF causes acute hepatitis and spontaneous abortion in infected livestock, leading to steep mortality rates and substantial economic losses. Once authorities declare an epidemic, they immediately prohibit all animal exports. Such bans cause further economic hardship, particularly for devel-



Laboratory evaluation of the RVF virus assay.

*Photo courtesy of Capt. Elizabeth Wanja*



Mosquitoes collected in Kenya during RVF field work.

*Photo by Lt. Col. Jason Richardson*





oping countries dependent on livestock for their livelihood. For Somalia, where livestock accounts for more than 80 percent of export earnings, extended bans can be devastating. Losses totaled US\$109 million during a ban there from February 1998 to May 1999 and another US\$326 million from September 2000 to December 2002.

Sick livestock infect other mosquito species, which then transmit the virus to humans. People can also contract RVF by coming into contact with the meat or blood of infected animals.

Mild cases of human RVF present with flu-like symptoms. In some cases, the patient can develop retinal degeneration, which may lead to blindness, and in severe cases, the patient can develop encephalitis or even hemorrhagic complications, which kill up to half of those who contract it.

In 1997, 300 Kenyans died from what researchers suspect was a hemorrhagic form of RVF. Determining actual infection rates on the African continent can

be challenging as populations often live far from medical care. No treatments or licensed vaccines exist for human RVF, only palliative care; thus, accurate and reliable diagnostic methods are critical.

The new test kit—developed by VecTOR with funding from the Small Business Innovation Research program and field testing funded by MIDRP—is a handheld dipstick assay that determines whether field-collected mosquitoes are infected with RVF virus. Providing results in less than 20 minutes, it is easy to use and does not require the use of a laboratory with containment facilities. Another advantage is that the test does not require refrigeration, a particular concern in the tropics. As long as the dipsticks are kept within their original containers, they remain stable for two or more years. Each RVF kit contains 50 tests and related materials, at a cost of \$8.00 apiece.

The test kits allow early detection of infected mosquitoes, which enables military planners and public health

officials to initiate preventive action, including mosquito control operations, administering animal vaccines, restricting the movement of livestock, and warning against contact with infected animals. Officials can also distribute mosquito nets and repellents to the public and forewarn local hospitals. On the military side, relevant agencies can issue proven preventive measures such as repellent and insecticide-treated uniforms and netting. Forces at increased risk include personnel operating in the Horn of Africa as part of Operation Enduring Freedom to combat terrorism and to thwart piracy.

The validation process for VecTOR's RVF virus assay was a joint effort among researchers from the Entomology Branch, Walter Reed Army Institute of Research; Virology Division, the U.S. Army Medical Research Institute of Infectious Diseases; the Kenyan Medical Research Institute; and the U.S. Army Medical Research Unit, Kenya.

## In the Works

The Entomology Branch at WRAIR and Virology Division at USAMRIID have been working on two other vector diagnostic assays developed by VecTOR to test for pathogens in mosquitoes and sand flies. One is a dipstick assay used to determine whether *Aedes* mosquitoes are infected with any of the four dengue virus serotypes known to cause disease in humans; the other is the leishmania dipstick, used to determine if sand flies are infected with *Leishmania major* pathogens.

Each assay has undergone extensive evaluation and has successfully fulfilled all laboratory and field diagnostic performance requirements. WRAIR and USAMRIID will present test results to the Armed Forces Pest Management Board. Hopes are that both assays will receive a national stock number and be available to deployed units in 2012.

WRAIR's Entomology Branch is working with

the Armed Forces Health Surveillance Center, Defense Threat Reduction Agency, and Chemical-Biological Medical Systems to improve vector-borne disease surveillance, detection, and response systems in both the DoD and global health communities. Through innovative translational research and product development efforts, the team is playing a vital part in the effort to predict, prevent, and respond to emerging and endemic disease threats.

*Lt. Col. Jason Richardson, WRAIR*  
*Dr. Michael Turell, USAMRIID*  
*Capt. Elizabeth Wanja, WRAIR*

## About the Authors

Lt. Col. Jason Richardson is the director of the Entomology Branch at WRAIR, where he leads a team of researchers developing tools to protect deployed personnel from vector-borne diseases, including malaria, dengue, leishmaniasis, and RVF. He was stationed in Kenya at USAMRU-K during the last major

RVF outbreak there in 2006–2007. He has been in the Army 17 years.

Dr. Michael Turell has been a research entomologist in the Virology Division at USAMRIID for 30 years. His research focuses on determining which mosquitoes can transmit which viruses as well as the factors affecting a mosquito's ability to transmit highly pathogenic viruses. In addition, he has helped develop diagnostic assays, evaluate live-attenuated viral vaccines, and conducted field studies in South/Central America and Africa. Turell served as an Army captain in the 1970s.

Capt. Elizabeth Wanja is a research entomologist of the Entomology Branch at WRAIR. Her research focuses on developing products for vector control, including evaluating attractants for insect vectors as well as developing diagnostic tools for vector-borne disease pathogens. Wanja has served in the Army for nearly eight years.

# USAMMCE Hosts German Military for Professional Development

The U.S. Army Medical Materiel Center, Europe hosted 17 Soldiers from the German Army Medical Supply and Maintenance Depot, located in Pfungstadt, Germany, for a Professional Development Day June 9.

The German Depot was activated July 1, 2008, as part of a Bundeswehr reorganization initiative and took over the mission of the former Medical Depot in Lorsch. It is headquartered by the Medical Command II (SanKdoII) located in Dietz, Germany. The Medical Depot in Pfungstadt consists of approximately 128 Soldiers and seven civilians and supplies 60,000 troops in four German states and deployed units in Afghanistan and Kosovo, as well as German Soldiers stationed in the United States at Holoman Air Force Base, N.M.; Luke AFB, Ariz.; Fort Bliss, Texas; Canada; and Sardinia.

Upon arrival, the group was welcomed by USAMMCE commander Col. William M. Stubbs. The deputy commander for Operations, Lt. Col. Douglas Galuszka, gave the Soldiers an overview of the USAMMCE mission, and USAMMCE TEWLS experts demonstrated the TEWLS operating system, followed by a tour through the different divisions and warehouses.

Oberfeldweibel (1st Sgt. and Training Non-Commissioned Officer) Tina Lehnhaeuser said, "I am very impressed with the TEWLS system and what it can do in the warehouse, especially the handheld scanners are a big help." The German Depot also works with a SAP-based system, but according to its users, this system is not as sophisticated as TEWLS.

After lunch, USAMMCE Soldiers introduced their German counterparts to the requirements for the Expert Field Medical Badge and demonstrated three EFMB tasks.

Later in the day, the German Soldiers were separated by Military Occupational Specialty and sent to the respective USAMMCE divisions to perform hands-on training.

The Maintenance NCO, Air Force Chief Master Sgt. Klaus Henrikus, explained that the technology for calibrating and repairing medical equipment and shop operations are the same on both sides and that they work on American equipment as well.

Before departing, company commander HPT Capt. Stephan Schledt said, "Everything is very impressive and you have top-notch technology, which makes everything faster and easier."

Both commanders agreed there will be more Professional Development Days and cultural exchanges in the future to strengthen the German/American partnership.

*Doris Crittenden*  
USAMMCE

## USAISR

### Promotions

#### June

Lt. Col. Andrew Peter Cap  
Lt. Col. Kevin Kee Chung  
Spc. Jeremy Neil Taylor

#### July

Staff Sgt. Robert Dewitt Dixon  
Capt. Stephanie K. Kessinger  
Spc. Cedric Stephon Mason

#### August

Sgt. Logan Michael Haller  
Staff Sgt. Tony Eugene Hill  
Capt. Jessica L. Slack

#### September

Staff Sgt. Joseph Anthony Holtz  
Staff Sgt. Shaun Michael Hurtado  
Staff Sgt. Maria Sue Thomas

## USAMRICD

### Promotions

#### June

Spc. Erik Byron Eaton, Jr.

#### July

Spc. Francisco Javier Calderon  
Master Sgt. Carlos Demone Wright

#### August

Sgt. Sheena Renee Pena

### Awards

#### August

#### Army Commendation Medal

Sgt. Erin Bouligny

#### Army Achievement Medal

Spc. Sharifq Baksh

#### Military Outstanding Voluntary Service Medal

Sgt. Erin Bouligny

#### Certificate of Achievement

Sgt. Erin Bouligny  
Sgt. (P) Nydia Reyes  
Spc. Cheryl Schenck





# WRAIR

## Awards

### July

#### Time Off Award

Ruthie Ratcliffe

#### Special Act Award

Carolyn Hales  
Nalo Merriman  
Amy Michels  
Roberta Nicoletta  
Brandon Whitfield

#### Supervisor Bonus

Carl Alving  
Thomas Balkin  
Robert Gramzinski  
Mary Marovich  
Paul Scott  
Frank Tortella  
Joan Zahn

### August

#### Army Commendation Medal

Lt. Col. Chunlin Zhang

#### Meritorious Service Medal

Maj. Charles A. Ditusa  
Maj. Charlotte A. Lanteri

## Army Achievement Medal

Sp. Carlos J. Diaz

## Promotions

### June

Sgt. Reginald Deshawn Acklin  
Sp. Jesus Alonzo Castro  
Col. James Francis Cummings  
Maj. Marlene Eroica Gubata  
Col. Thomas George Oliver  
Maj. Kristopher Mark Paolino  
Sgt. 1st Class Chester Allan Stugus, Jr.

### July

Sp. Julio Cesar Careagabaria  
Staff Sgt. Erik Ryan Pollender  
Maj. Michael J. Superior

### August

Sp. Andrea Minga Duarte  
Sp. Jasmina Renea Hughson  
Staff Sgt. Rubinel Rivera  
Maj. Cyruss Antonio Por Tsurgeon

# USAARL

## Awards

### June

#### Chief of Staff of the Army

#### Certificate of Appreciation

Col. Stephan Bernstein

#### Distinguished/Honorary Members of the Regiment Award

Col. Stephan Bernstein

#### Presidential Certificate of Appreciation

Col. Stephan Bernstein

#### Order of Military Medical Merit

Col. Stephan Bernstein

#### Legion of Merit

Col. Stephan Bernstein

#### Army Commendation Medal

Sp. Adam Thompson

### July

#### Army Achievement Medal

Sp. Adam Thompson

### August

#### Certificate of Appreciation

Dani Mitchell

#### Commander's Award for Civilian Service

Jean Southwell

### September

#### Army Achievement Medal

Sp. Elise Corrado

## Certificate of Appreciation

Sp. Jinyong Bae  
Kelley Beavers  
Scott Childress  
Deahndra Grigley  
Tyronne Leonard  
Pfc. Monica Manalo  
Tammy Tate  
Catherine Webb

## Certificate of Achievement

Catherine Machen

## Meritorious Performance of Duty Award

Dr. Heber Jones

## Commander's Award for Civilian Service

Dr. Lori St. Onge

## 25 Years of Service Award

Diana Hemphill

## 15 Years of Service Award

Victor Estes

## Promotions

### June

Sgt. Kathleen Erin Kelley  
Sp. Summer Joy Megumi Nomura

### July

Sgt. Adam Thompson

# USAMRIID

## Promotions

### June

Sgt. Michael Garrett Lavorgna  
Staff Sgt. Anita J S Teadt

### July

Sp. Opakirite Owunari Benebo  
Sp. Mari Lynn Short

### August

Lt. Col. Michael Forrest Ingram  
Sp. Amy Miekko Hasegawa

### September

Lt. Col. Carrie Grum Benton  
Sgt. Darnell Reshaun Pierce  
Lt. Col. Douglas L. Stratton  
Sgt. Christopher Eugene Terry

# USAMMA

## Promotions

### July

Staff Sgt. Joshua Caleb Reynolds

### August

Sgt. Christian Porr

### September

Staff Sgt. Harland Eugene Wells

# USAMMCE

## Promotion

### July

Sp. Jason Timothy Roth

# HFAA

## Promotions

### July

Capt. Daniel C. Davis  
Capt. John Heniger

### September

Lt. Col. Philip Christop Knightshean

# USAMRMC

## Promotions

### June

Sgt. 1st Class Keith Charles Hall

### July

Capt. Bruce W. Barnes  
Master Sgt. Mark Allen Reynolds